WEST Search History

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DATE: Tuesday, October 30, 2007

Hide?	Set Name	Query	Hit Count
		DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR	
☐	L36	L33 and (HARP)adj(factor)	0
☐	L35	L33 and 13-39	0
☐	L34	L33 and AECKYQFQAWGECDLNTALK	0
☐	L33	L32 and inhibit?	177
☐	L32	L30 and (angiogenesis)	255
☐	L31	L30 and (HARP)	4
☐	L30	424/185.1,530/324,300,350,435/69.1.ccls.	3057
☐	L29	L26 and pleiotrophin	5
☐	L28	L26 and (heparin)adj(affin)adj(regulatory)adj(peptide)	0
☐	L27	L26 and harp	4
☐	L26	424/185.1,530/324,300.ccls.	3057
☐	L25	(milhiet)adj(pierre)	3
☐	L24	(delbe)adj(jean)	3
☐	L23	(pierrot)adj(isabelle)	3
☐	L22	L21 and harp	8
☐	L21	(barritault)adj(denis)	40
☐	L20	L19 and harp	8
☐	L19	(courty)adj(jose)	16
☐	L18	L5 and glycoaminoglycans	1
☐	L17	l9 and glycoaminoglycans	1
☐	L16	L15 and glycoaminoglycans	1
☐	L15	(heparin)adj(binding)adj(growth)adj(associated)adj(molecule)	63
☐	L14	L12 and (glucoaminoglycans)	0
☐	L13	L12 and (binds)adj(glucoaminoglycans)	0
☐	L12	(heparin)adj(binding)adj(growth)adj(associated)adj(molecule)	63
☐	L11	L10 and (inhibit)adj(angiogenesis)	40
☐	L10	L9 and fragment	463
☐	L9	pleiotrophin	603
☐	L8	HB-CAM	0
☐	L7	L6 not @ay>"2002"	28
☐	L6	L5 and (inhibit)same(angiogenesis)	63

☐	L5	HARP	5924
☐	L4	L3 and (inhibit)adj(angiogenesis)	1
☐	L3	(heparin)adj(affin)adj(regulatory)adj(peptide)	15
	DB=USPT; PLUR=YES; OP=OR		
☐	L2	6103880.pn.	1
☐	L1	5641743.pn.	1

END OF SEARCH HISTORY

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NEWS 6	JUL 16	CAplus enhanced with French and German abstracts
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=> s "HARP"
L1         3077 "HARP"

=> s l1 and heparin affin regulatory peptide
L2          150 L1 AND HEPARIN AFFIN REGULATORY PEPTIDE

=> s l2 and pleiotrophin
L3          101 L2 AND PLEIOTROPHIN

=> s l3 and inhibit angiogenesis
L4            4 L3 AND INHIBIT ANGIOGENESIS

=> dup remove l4
PROCESSING COMPLETED FOR L4
L5             2 DUP REMOVE L4 (2 DUPLICATES REMOVED)

=> d l5 1-2 cbib abs

L5   ANSWER 1 OF 2     MEDLINE on STN                    DUPLICATE 1
2004302962.    PubMed ID: 15203110.   Identification of heparin
     affin regulatory peptide domains with
     potential role on angiogenesis. Polykratis Apostolos; Delbe Jean; Courty
     Jose; Papadimitriou Evangelia; Katsoris Panagiotis. (Laboratory of
     Molecular Pharmacology, Department of Pharmacy, University of Patras,
     Patras, GR 26504, Greece. ) The international journal of biochemistry &
     cell biology, (2004 Oct) Vol. 36, No. 10, pp. 1954-66.  Journal code:
     9508482. ISSN: 1357-2725. Pub. country: England: United Kingdom. Language:
     English.
AB   Heparin affin regulatory peptide (
     HARP) is a growth factor displaying high affinity for heparin.  It
     is present in the extracellular matrix of many tissues, interacting with
     heparan sulfate and dermatan/chondroitin sulfate glycosaminoglycans.  We
     have previously shown that HARP is implicated in the control of
     angiogenesis and its effects are mimicked, at least in part, by synthetic
     peptides that correspond to its N and C termini.  In the present work, we
     show that HARP is cleaved by plasmin, leading to the production
     of five peptides that correspond to distinct domains of the molecule.
     Heparin, heparan sulfate and dermatan sulfate, at various HARP
     to glycosaminoglycan ratios, partially protect HARP from plasmin
     degradation.  The molecules with higher affinity to HARP are the
```

more protective, heparin being the most efficient. The peptides that are produced from cleavage of **HARP** by plasmin, affect in vivo and in vitro angiogenesis and modulate the angiogenic activity of vascular endothelial growth factor on human umbilical vein endothelial cells. Similar results were obtained in vitro with recombinant **HARP** peptides, identical to the peptides generated after treatment of **HARP** with plasmin. These results suggest that different regions of **HARP** may induce or **inhibit angiogenesis.**

L5 ANSWER 2 OF 2 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN DUPLICATE 2

2004113415 EMBASE A Synthetic Peptide that Corresponds to the C-terminal Region of **HARP Inhibits Angiogenesis** in vivo and in vitro. Mikelis K.; Polykratis A.; Zompra A.; Cordopatis P.; Katsoris P.; Courty J.; Papadimitriou E.. K. Mikelis, Lab. of Molecular Pharmacology, Dept. of Pharmacy, University of Patras, Patra, GR 26504, Greece. Review of Clinical Pharmacology and Pharmacokinetics, International Edition Vol. 18, No. 1, pp. 144-145 2004.
Refs: 9.
ISSN: 1011-6583. CODEN: EKIEE2
Pub. Country: Greece. Language: English. Summary Language: English.
Entered STN: 20040412. Last Updated on STN: 20040412

AB **Heparin Affin Regulatory Peptide** (**HARP**), also known as **pleiotrophin** or heparin-binding growth-associated molecule, is an 18 kDa growth factor that has a high affinity for heparin. In the present work, we studied the effects of a synthetic peptide that corresponds to the last 25 amino-acids of the C-terminal region. In the in vivo chicken embryo chorioallantoic membrane model of angiogenesis, the peptide decreased the number of blood vessels in a dose-dependent manner. It also decreased the migration of human umbilical vein endothelial cells (HUVEC) in vitro, while it had no effect on HUVEC proliferation. Finally, the peptide also decreased the ability of HUVEC to form capillary-like networks when cultured on matrigel.

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=> s l2 and fragment
L6            3 L2 AND FRAGMENT

=> dup remove l6
PROCESSING COMPLETED FOR L6
L7             2 DUP REMOVE L6 (1 DUPLICATE REMOVED)

=> s l7 and pd<20021030
   1 FILES SEARCHED...
   4 FILES SEARCHED...
L8            1 L7 AND PD<20021030

=> d l8 cbib abs
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L8 ANSWER 1 OF 1 MEDLINE on STN

2002452367. PubMed ID: 12070152. Dominant negative effectors of **heparin affin regulatory peptide** (**HARP**) angiogenic and transforming activities. Bernard-Pierrot Isabelle; Delbe Jean; Rouet Vincent; Vigny Marc; Kerros Marie-Emmanuelle; Caruelle Daniele; Raulais Daniel; Barritault Denis; Courty Jose; Milhiet Pierre Emmanuel. (Laboratoire de recherche sur la Croissance Cellulaire, la Reparation et la Regeneration Tissulaires (CRRET), CNRS UPRES-A 7053, Universite Paris XII, Avenue du General de Gaulle, 94010 Creteil Cedex, France.) The Journal of biological chemistry, **(2002 Aug 30)** Vol. 277, No. 35, pp. 32071-7. Electronic Publication: 2002-06-17.
Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States.
Language: English.

AB **Heparin affin regulatory peptide** (**HARP**) is an heparin-binding growth factor, highly expressed in several primary human tumors and considered as a rate-limiting angiogenic

factor in tumor growth, invasion, and metastasis. Implication of this protein in carcinogenesis is linked to its mitogenic, angiogenic, and transforming activities. Recently, we have demonstrated that the C-terminal residues 111-136 of **HARP** are required for its mitogenic and transforming activities (Bernard-Pierrot, I., Delbe, J., Caruelle, D., Barritault, D., Courty, J., and Milhiet, P. E. (2001) J. Biol. Chemical 276, 12228-12234). In this paper, **HARP** deleted of its last 26 amino acids was shown to act as a dominant negative effector for its mitogenic, angiogenic, transforming, and tumor-formation activities by heterodimerizing with the wild type protein. Similarly, the synthetic corresponding peptide P111-136 displayed in vitro inhibition of wild type **HARP** activities, but in this case, the inhibition was mainly explained by the competition of the peptide with **HARP** for the binding to the extracellular domain of the high affinity ALK receptor.

```
=> s l2 and derivative
L9            0 L2 AND DERIVATIVE

=> s l2 and fragment
L10           3 L2 AND FRAGMENT

=> s l10 and inhibit angiogenesis
L11           1 L10 AND INHIBIT ANGIOGENESIS

=> d l11 cbib abs

L11  ANSWER 1 OF 1     MEDLINE on STN
2004302962.    PubMed ID: 15203110.   Identification of heparin
     affin regulatory peptide domains with
     potential role on angiogenesis. Polykratis Apostolos; Delbe Jean; Courty
     Jose; Papadimitriou Evangelia; Katsoris Panagiotis. (Laboratory of
     Molecular Pharmacology, Department of Pharmacy, University of Patras,
     Patras, GR 26504, Greece. ) The international journal of biochemistry &
     cell biology, (2004 Oct) Vol. 36, No. 10, pp. 1954-66.  Journal code:
     9508482. ISSN: 1357-2725. Pub. country: England: United Kingdom. Language:
     English.
AB   Heparin affin regulatory peptide (
     HARP) is a growth factor displaying high affinity for heparin.  It
     is present in the extracellular matrix of many tissues, interacting with
     heparan sulfate and dermatan/chondroitin sulfate glycosaminoglycans.  We
     have previously shown that HARP is implicated in the control of
     angiogenesis and its effects are mimicked, at least in part, by synthetic
     peptides that correspond to its N and C termini.  In the present work, we
     show that HARP is cleaved by plasmin, leading to the production
     of five peptides that correspond to distinct domains of the molecule.
     Heparin, heparan sulfate and dermatan sulfate, at various HARP
     to glycosaminoglycan ratios, partially protect HARP from plasmin
     degradation.  The molecules with higher affinity to HARP are the
     more protective, heparin being the most efficient.  The peptides that are
     produced from cleavage of HARP by plasmin, affect in vivo and in
     vitro angiogenesis and modulate the angiogenic activity of vascular
     endothelial growth factor on human umbilical vein endothelial cells.
     Similar results were obtained in vitro with recombinant HARP
     peptides, identical to the peptides generated after treatment of
     HARP with plasmin.  These results suggest that different regions
     of HARP may induce or inhibit angiogenesis.

=> s "HB-CAM"
L12           1 "HB-CAM"

=> d l12 cbib abs

L12  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2007 ACS on STN
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1992:564723 Document No. 117:164723 Cell density-dependent expression of heparin-binding growth-associated molecule (HB-GAM, p18) and its down-regulation by fibroblast growth factors. Merenmies, Jussi (Inst. Biotechnol., Univ. Helsinki, Helsinki, 00380, Finland). FEBS Letters, 307(3), 297-300 (English) 1992. CODEN: FEBLAL. ISSN: 0014-5793.
AB Heparin-binding growth-associated mol. (HB-GAM) is a developmentally regulated protein that is intensely expressed during the rapid postnatal growth phase of rat brain. The expression of HB-GAM studied in 12 cell lines was restricted to C6 rat glioma cell line and BALB/c 3T3 cells. In BALB/c 3T3 cells the expression of HB-GAM was enhanced in confluent and quiescent cell cultures. When the confluent cultures were treated with bFGF the expression of HB-GAM mRNA was strongly reduced and the protein disappeared rapidly from proliferating cells. The data presented suggest involvement of **HB-CAM** in cell differentiation phenomena rather than in cell proliferation.

=> s l1 and "13-39"
L13 4 L1 AND "13-39"

=> s l13 and pd<20021030
2 FILES SEARCHED...
L14 0 L13 AND PD<20021030

=> dup remove l13
PROCESSING COMPLETED FOR L13
L15 3 DUP REMOVE L13 (1 DUPLICATE REMOVED)

=> d l15 1-3 cbib abs

L15 ANSWER 1 OF 3 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2007:37683 Document No.: PREV200700040206. On the interventional role of eNOS in hydrogen peroxide-induced **HARP**/pleiotrophin up-regulation in endothelial cells. Polytarchou, C. [Reprint Author]; Hatziapostolou, M.; Papadimitriou, E.. Univ Patras, Dept Pharm, Mol Pharmacol Lab, GR-26110 Patras, Greece. cpolyt@upatras.gr; hatziap@upatras.gr; epapad@upatras.gr. FEBS Journal, (JUN 2006) Vol. 273, No. Suppl. 1, pp. 149.
Meeting Info.: 31st Congress of the Federation-of-European-Biochemical-Societies (FEBS). Istanbul, TURKEY. June 24 -29, 2006. Federat European Biochem Soc.
ISSN: 1742-464X. E-ISSN: 1742-4658. Language: English.

L15 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
2004:370799 Document No. 140:386013 Angiogenesis-inhibiting **HARP** factor peptide fragments. Courty, Jose; Barritault, Denis; Bernard Pierrot, Isabelle Christine; Delbe, Jean Camille Georges; Milhiet, Pierre Emmanuel (Centre National de la Recherche Scientifique CNRS, Fr.). Fr. Demande FR 2846659 A1 20040507, 36 pp. (French). CODEN: FRXXBL.
APPLICATION: FR 2002-13621 20021030.
AB The invention relates to peptide fragments **13-39** and 65-97 of the factor **HARP**, which inhibit angiogenesis. In an advantageous way, these peptides can be peptide 111-136 of **HARP**. The invention also relates to pharmaceutical compns. including these peptides or of the nucleic acids coding for these peptides, and their uses for the treatment of pathologies associated with angiogenesis, in particular proliferative disorders like cancer.

L15 ANSWER 3 OF 3 MEDLINE on STN DUPLICATE 1
2004546242. PubMed ID: 15517900. X-rays affect the expression of genes involved in angiogenesis. Polytarchou C; Gligoris T; Kardamakis D; Kotsaki E; Papadimitriou E. (Laboratory of Molecular Pharmacology, Department of Pharmacy, School of Health Sciences, University of Patras, GR 26504, Greece.) Anticancer research, (2004 Sep-Oct) Vol. 24, No. 5A, pp. 2941-5.
Journal code: 8102988. ISSN: 0250-7005. Pub. country: Greece. Language: English.

AB BACKGROUND: We have previously shown, using the chicken embryo chorioallantoic membrane (CAM) model of in vivo angiogenesis, that X-rays act on the extracellular matrix and enhance normal and tumor-induced angiogenesis. In the present work, we studied the effect of X-rays on the gene expression of three proteins that are important regulators of angiogenesis: vascular endothelial growth factor (VEGF), heparin affin regulatory peptide (**HARP**) and inducible nitric oxide synthase (iNOS). MATERIALS AND METHODS: An area of 1 cm2 of the CAM, restricted by a plastic ring was irradiated at room temperature. The expression of the genes was studied using RT-PCR and the amounts of the mRNAs were quantified using image analysis of the corresponding agarose gels of the RT-PCR products. RESULTS: VEGF mRNA was decreased 6 h after irradiation. However, at later time points, VEGF expression was significantly increased compared with the nonirradiated tissue. Similarly, X-rays down-regulated both **HARP** and iNOS expression 6 h after irradiation and the effect was reversed at later time points, similarly to the effect of X-rays on VEGF. CONCLUSION: These data support the notion that X-rays increase the expression of genes that favor angiogenesis.

=> s l1 and "65-97"
L16 1 L1 AND "65-97"

=> d l16 cbib abs

L16 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN
2004:370799 Document No. 140:386013 Angiogenesis-inhibiting **HARP** factor peptide fragments. Courty, Jose; Barritault, Denis; Bernard Pierrot, Isabelle Christine; Delbe, Jean Camille Georges; Milhiet, Pierre Emmanuel (Centre National de la Recherche Scientifique CNRS, Fr.). Fr. Demande FR 2846659 A1 20040507, 36 pp. (French). CODEN: FRXXBL. APPLICATION: FR 2002-13621 20021030.
AB The invention relates to peptide fragments 13-39 and **65-97** of the factor **HARP**, which inhibit angiogenesis. In an advantageous way, these peptides can be peptide 111-136 of **HARP**. The invention also relates to pharmaceutical compns. including these peptides or of the nucleic acids coding for these peptides, and their uses for the treatment of pathologies associated with angiogenesis, in particular proliferative disorders like cancer.

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L17 11 L1 AND "111-136"

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ENTER REMOVE, IDENTIFY, ONLY, OR (?):remove
'REOVE' IS NOT VALID. VALID FILE NAMES ARE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS'
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PROCESSING COMPLETED FOR L17
L18 3 DUP REMOVE L17 (8 DUPLICATES REMOVED)

=> d l18 1-3 cbib abs

L18 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
2004:370799 Document No. 140:386013 Angiogenesis-inhibiting **HARP** factor peptide fragments. Courty, Jose; Barritault, Denis; Bernard Pierrot, Isabelle Christine; Delbe, Jean Camille Georges; Milhiet, Pierre Emmanuel (Centre National de la Recherche Scientifique CNRS, Fr.). Fr. Demande FR 2846659 A1 20040507, 36 pp. (French). CODEN: FRXXBL.

APPLICATION: FR 2002-13621 20021030.

AB The invention relates to peptide fragments 13-39 and 65-97 of the factor **HARP**, which inhibit angiogenesis. In an advantageous way, these peptides can be peptide **111-136** of **HARP**. The invention also relates to pharmaceutical compns. including these peptides or of the nucleic acids coding for these peptides, and their uses for the treatment of pathologies associated with angiogenesis, in particular proliferative disorders like cancer.

L18 ANSWER 2 OF 3 MEDLINE on STN DUPLICATE 1

2002452367. PubMed ID: 12070152. Dominant negative effectors of heparin affin regulatory peptide (**HARP**) angiogenic and transforming activities. Bernard-Pierrot Isabelle; Delbe Jean; Rouet Vincent; Vigny Marc; Kerros Marie-Emmanuelle; Caruelle Daniele; Raulais Daniel; Barritault Denis; Courty Jose; Milhiet Pierre Emmanuel. (Laboratoire de recherche sur la Croissance Cellulaire, la Reparation et la Regeneration Tissulaires (CRRET), CNRS UPRES-A 7053, Universite Paris XII, Avenue du General de Gaulle, 94010 Creteil Cedex, France.) The Journal of biological chemistry, (2002 Aug 30) Vol. 277, No. 35, pp. 32071-7. Electronic Publication: 2002-06-17. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Heparin affin regulatory peptide (**HARP**) is an heparin-binding growth factor, highly expressed in several primary human tumors and considered as a rate-limiting angiogenic factor in tumor growth, invasion, and metastasis. Implication of this protein in carcinogenesis is linked to its mitogenic, angiogenic, and transforming activities. Recently, we have demonstrated that the C-terminal residues **111-136** of **HARP** are required for its mitogenic and transforming activities (Bernard-Pierrot, I., Delbe, J., Caruelle, D., Barritault, D., Courty, J., and Milhiet, P. E. (2001) J. Biol. Chemical 276, 12228-12234). In this paper, **HARP** deleted of its last 26 amino acids was shown to act as a dominant negative effector for its mitogenic, angiogenic, transforming, and tumor-formation activities by heterodimerizing with the wild type protein. Similarly, the synthetic corresponding peptide P111-136 displayed in vitro inhibition of wild type **HARP** activities, but in this case, the inhibition was mainly explained by the competition of the peptide with **HARP** for the binding to the extracellular domain of the high affinity ALK receptor.

L18 ANSWER 3 OF 3 MEDLINE on STN DUPLICATE 2

2001287580. PubMed ID: 11150308. The lysine-rich C-terminal tail of heparin affin regulatory peptide is required for mitogenic and tumor formation activities. Bernard-Pierrot I; Delbe J; Caruelle D; Barritault D; Courty J; Milhiet P E. (Laboratoire de Recherche sur la Croissance Cellulaire, la Reparation et la Regeneration Tissulaires, CNRS UPRES-A 7053, Universite Paris XII, Avenue du General de Gaulle, 94010 Creteil Cedex, France.) The Journal of biological chemistry, (2001 Apr 13) Vol. 276, No. 15, pp. 12228-34. Electronic Publication: 2001-01-09. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Heparin affin regulatory peptide (**HARP**) is a 18-kDa heparin-binding polypeptide that is highly expressed in developing tissues and in several primary human tumors. It seems to play a key role in cellular growth and differentiation. In vitro, **HARP** displays mitogenic, angiogenic, and neurite outgrowth activities. It is a secreted protein that is organized in two beta-sheet domains, each domain containing a cluster of basic residues. To assess determinants involved in the biological activities of **HARP**, C-terminally truncated proteins were produced in Chinese hamster ovary-K1 cells and tested for their mitogenic, tumor formation in nude mice and neurite outgrowth activities. Our data clearly indicate that the residues **111-136** of the lysine-rich C-terminal domain are involved in the mitogenic and tumor formation activities of **HARP**. Correlatively, no signal transduction was detected using the corresponding mutant, suggesting the absence of **HARP** binding to its high

affinity receptor. However, this C-terminal domain of **HARP** is not involved in the neurite outgrowth activity. We also demonstrate that **HARP** signal peptide cleavage could led to two maturated forms that are both but differentially mitogenic.

```
=> s pleiotrophin
L19       2320 PLEIOTROPHIN

=> s l19 and fragment
L20        122 L19 AND FRAGMENT

=> s l20 and inhibits
L21          3 L20 AND INHIBITS

=> dup remove l21
PROCESSING COMPLETED FOR L21
L22          3 DUP REMOVE L21 (0 DUPLICATES REMOVED)

=> d l22 1-3 cbib abs
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L22 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
2005:1020555 Document No. 143:320266 Genes with differential expression profile between human dental pulp stem cells and mesenchymal stem cells and use for regenerating tooth germ. Ueda, Minoru; Yamada, Yoichi (Hitachi Medical Corp., Japan). Jpn. Kokai Tokkyo Koho JP 2005253442 A 20050922, 246 pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 2004-111582 20040309.

AB The present invention relates to a group of genes whose expression profile are different between human dental pulp stem cells and mesenchymal stem cells, as well as a method for regenerating tooth germ using these genes. According to the present invention, the gene expression profiles and cluster anal. between human dental pulp stem cells (hDPSCs) and mesenchymal stem cells (hMSCs) as representative populations of odontoprogenitor and osteoprogenitor cell were revealed, and a group of genes whose expression profile are different between human dental pulp stem cells and mesenchymal stem cells was identified. By utilizing the groups of the genes of the present invention together with the dental pulp stem cells and mesenchymal stem cells, hard tissue such as tooth germ, dental pulp, dentin or bone can be regenerated. The present inventors investigated the gene expression profiles and cluster anal. between human dental pulp stem cells (hDPSCs) and mesenchymal stem cells (hMSCs) as representative populations of odontoprogenitor and osteoprogenitor cells, resp. At first, the present inventors confirmed the differential expression of Alkaline phosphatase (ALP) activity, Dentin matrix protein 1 (DMP 1), Dentin phosphosialoprotein (DSPP) using by real time reverse-transcriptase polymerase chain reaction (RT-PCR) in total RNA from primary cultures. The number of genes in hDPSCs(I) that were up-regulated by 2>-fold, compared to hMSCs, was 614 (Table, IV). On the other band, the number of genes down regulated by <2-fold in hDPSCs (I) was 296 (Table III, IV).

L22 ANSWER 2 OF 3 MEDLINE on STN
2005486805. PubMed ID: 16156786. **Pleiotrophin inhibits** HIV infection by binding the cell surface-expressed nucleolin. Said Elias A; Courty Jose; Svab Josette; Delbe Jean; Krust Bernard; Hovanessian Ara G. (UPR 2228 CNRS, UFR Biomedicale des Saints-Peres, Paris, France.. elias.said@umontreal.ca) . The FEBS journal, (2005 Sep) Vol. 272, No. 18, pp. 4646-59. Journal code: 101229646. ISSN: 1742-464X. Pub. country: England: United Kingdom. Language: English.

AB The growth factor **pleiotrophin** (PTN) has been reported to bind heparan sulfate and nucleolin, two components of the cell surface implicated in the attachment of HIV-1 particles to cells. Here we show that PTN **inhibits** HIV-1 infection by its capacity to inhibit HIV-1 particle attachment to the surface of permissive cells. The

beta-sheet domains of PTN appear to be implicated in this inhibitory effect on the HIV infection, in particular the domain containing amino acids 60-110. PTN binding to the cell surface is mediated by high and low affinity binding sites. Other inhibitors of HIV attachment known to bind specifically surface expressed nucleolin, such as the pseudopeptide HB-19 and the cytokine midkine prevent the binding of PTN to its low affinity-binding site. Confocal immunofluorescence laser microscopy revealed that the cross-linking of surface-bound PTN with a specific antibody results in the clustering of cell surface-expressed nucleolin and the colocalization of both PTN and nucleolin signals. Following its binding to surface-nucleolin, PTN is internalized by a temperature sensitive mechanism, a process which is inhibited by HB-19 and is independent of heparan and chondroitin sulfate proteoglycans. Nevertheless, proteoglycans might play a role in the concentration of PTN on the cell surface for a more efficient interaction with nucleolin. Our results demonstrate for the first time that PTN **inhibits** HIV infection and suggest that the cell surface-expressed nucleolin is a low affinity receptor for PTN binding to cells and it is also implicated in PTN entry into cells by an active process.

L22 ANSWER 3 OF 3 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2006:180372 Document No.: PREV200600182484. Blocking **pleiotrophin** activity **inhibits** multiple myeloma (MM) cell growth in vitro and in a severe combined immunodeficient (SCID)-hu murine model of human MM. Campbell, Richard A. [Reprint Author]; Chen, Haiming; Lee, Hee Jin; Yeh, Howard S.; Gordon, Melinda S.; Bonavida, Benjamin; Pang, Shen; Said, Jonathan; Berenson, James R.. Inst Myeloma and Bone Canc Res, W Hollywood, CA USA. Blood, (NOV 16 2005) Vol. 106, No. 11, Part 1, pp. 37A. Meeting Info.: 47th Annual Meeting of the American-Society-of-Hematology. Atlanta, GA, USA. December 10 -13, 2005. Amer Soc Hematol. CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB **Pleiotrophin** (PTN) is a heparin-binding growth factor that binds CD138 and stimulates angiogenesis, tumor growth and metastasis in some solid tumors. Recently, we have shown that this factor is highly produced by multiple myeloma (MM) cell lines including RPMI8226 and U266 and fresh malignant plasma cells, and is secreted into the culture medium following short-term culture of bone marrow from MM patients. We investigated the effects of PTN on MM growth in vitro and in vivo using a SCID-hu murine MM model. We determined the antiproliferative effects of suppressing PTN by cloning a whole PTN sense or anti-sense cDNA construct containing the green fluorescent protein (GFP) gene into the MM cell lines RPMI8226 and U266. Cells transduced with sense PTN showed markedly increased proliferation compared to cells transduced with vector alone whereas the anti-sense-containing MM cells showed reduced cell numbers. In addition, we treated RPMI8226 and U266 cells with a polyclonal anti-PTN antibody and evaluated its effect on MM growth. These cells were cultured for 48 hours in the presence of the anti-PTN antibody at a concentration of 100 micrograms/ml or a control antibody, and effects on cell growth assessed with an MTT assay. Marked anti-MM effects were observed with the anti-PTN antibody compared to the control antibody in both cell lines [RPMI8226 ($p < 0.01$) and U266 ($p < 0.001$)]. In order to further define the importance of PTN in the growth of MM in a more clinically relevant in vivo setting, we determined whether this polyclonal anti-PTN antibody could suppress tumor growth and human paraprotein secretion using our SCID-hu murine model of human myeloma LAG lambda-1. LAG lambda-1 has been previously shown by our group to produce large amounts of PTN as measured in mouse serum by ELISA and by RT-PCR analysis on freshly isolated LA lambda-1 tumor cells. Thirty SCID mice ($n = 5$ mice/group) were implanted with a 0.4 - 0.6 cm(3) LAG lambda-1 tumor **fragment** into the left hind limb muscle. Fourteen days following implantation, mice were randomized into treatment groups, and received treatment intraperitoneally (IP) with anti-PTN antibody at doses of 0.1, 0.3, 1.0, 3.0 or 10 mg/kg or vehicle alone twice weekly. Mice receiving anti-PTN antibody at the highest doses (3.0 and 10 mg/kg) showed marked inhibition of tumor growth [3.0 mg/kg ($p < 0.03$), 10 mg/kg ($p < 0.008$)] as well as decreases in levels of human

paraprotein [3.0 mg/kg ($p < 0.004$), 10 mg/kg ($p < 0.003$)]. Notably, immumohistochemical staining with an anti-CD138 antibody showed a marked reduction in cells with CD138 positivity in the LAG lambda-1 tumors from animals treated with anti-PTN antibody compared to mice treated with vehicle alone. These in vitro and in vivo results demonstrate that PTN may be a potential new target for the treatment of MM. The effects of this therapy on angiogenesis and cell signaling are currently under investigation.

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=> s anaplastic lymphoma kinase
L23       2221 ANAPLASTIC LYMPHOMA KINASE

=> s l23 and inhibit
L24         57 L23 AND INHIBIT

=> s l24 and angiogenesis
L25          9 L24 AND ANGIOGENESIS

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PROCESSING COMPLETED FOR L25
L26          8 DUP REMOVE L25 (1 DUPLICATE REMOVED)

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L26 ANSWER 1 OF 8 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

2007225943 EMBASE Heat shock protein 90: The cancer chaperone. Neckers L.. L. Neckers, Urologic Oncology Branch, National Cancer Institute, Bethesda, MD 20892, United States. len@helix.nih.gov. Journal of Biosciences Vol. 32, No. 3, pp. 517-530 Apr 2007.
Refs: 122.
ISSN: 0250-5991. E-ISSN: 0250-5991. CODEN: JOBSDN
Pub. Country: India. Language: English. Summary Language: English.
Entered STN: 20070619. Last Updated on STN: 20070619

AB Heat shock protein 90 (Hsp90) is a molecular chaperone required for the stability and function of a number of conditionally activated and/or expressed signalling proteins, as well as multiple mutated, chimeric, and/or overexpressed signalling proteins, that promote cancer cell growth and/or survival. Hsp90 inhibitors are unique in that, although they are directed towards a specific molecular target, they simultaneously **inhibit** multiple cellular signalling pathways. By inhibiting nodal points in multiple overlapping survival pathways utilized by cancer cells, combination of an Hsp90 inhibitor with standard chemotherapeutic agents may dramatically increase the in vivo efficacy of the standard agent. Hsp90 inhibitors may circumvent the characteristic genetic plasticity that has allowed cancer cells to eventually evade the toxic effects of most molecularly targeted agents. The mechanism-based use of Hsp90 inhibitors, both alone and in combination with other drugs, should be effective toward multiple forms of cancer. Further, because Hsp90 inhibitors also induce Hsf-1-dependent expression of Hsp70, and because certain mutated Hsp90 client proteins are neurotoxic, these drugs display ameliorative properties in several neurodegenerative disease models, suggesting a novel role for Hsp90 inhibitors in treating multiple pathologies involving neurodegeneration. .COPYRGT. Indian Academy of Sciences.

L26 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN

2006:164596 Document No. 144:226266 Pleiotrophin-based reagents for regulating cell differentiation and treatment of multiple myeloma. Berenson, James; Haiming, Chen; Gordon, Melinda S. (Institute for Multiple Myeloma and Bone Cancer Research, USA). PCT Int. Appl. WO 2006020684 A2 20060223, 111 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG,

KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2005-US28362 20050810. PRIORITY: US 2004-600132P 20040810.

AB The present invention is based on the discovery that pleiotrophin, a secreted factor produced by multiple myeloma cells, other cancer cells, and bone marrow stromal cells, induces monocyte/macrophages to trans-differentiation into endothelial-like cells. Pleiotrophin receptors are also found on multiple myeloma cells, including CD138, receptor protein tyrosine kinase phosphatase β/ζ, syndecan 3, and ALK (**anaplastic lymphoma kinase**), and the levels of pleiotrophin and its receptors are markedly elevated in multiple myeloma patients as compared to the normal control group, indicating that pleiotrophin-mediated cellular differentiation plays a fundamental role in multiple myeloma. In addition, pleiotrophin induces pluripotent stem cells to differentiate into endothelial-like cells, and pleiotrophin has vasculogenic activity for bone marrow stem cells. Thus, pleiotrophin is a key mol. regulating cellular processes, e.g., trans-differentiation and **angiogenesis**, associated with tumorigenesis, including multiple myeloma. Tumor growth and development, and related **angiogenesis** , is inhibited by treatment with agents (antisense mols. or antibodies) that **inhibit** or reduce pleiotrophin activity. Thus, the present invention provides methods of regulating cellular differentiation, including differentiation of stem cells and trans-differentiation of monocytes/macrophages using agonists or antagonists of pleiotrophin or a pleiotrophin receptor, as well as related methods of treating cancers associated with pleiotrophin-regulated differentiation and **angiogenesis**, including, e.g., multiple myeloma.

L26 ANSWER 3 OF 8 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

2006:730516 The Genuine Article (R) Number: 066OW. RNA interference-mediated gene silencing of pleiotrophin through polyethylenimine-complexed small interfering RNAs in vivo exerts antitumoral effects in glioblastoma xenografts. Grzelinski M; Urban-Klein B; Martens T; Lamszus K; Bakowsky U; Hobel S; Czubayko F; Aigner A (Reprint). Univ Marburg, Sch Med, Dept Pharmacol & Toxicol, Karl v Frisch Str 1, D-35033 Marburg, Germany (Reprint); Univ Marburg, Sch Med, Dept Pharmacol & Toxicol, D-35033 Marburg, Germany; Univ Hamburg, Hosp Eppendorf, Dept Neurosurg, D-20246 Hamburg, Germany; Univ Marburg, Sch Med, Dept Biopharm & Pharmaceut Technol, D-35033 Marburg, Germany. aigner@staff.uni-marburg.de. HUMAN GENE THERAPY (JUL 2006) Vol. 17, No. 7, pp. 751-766. ISSN: 1043-0342. Publisher: MARY ANN LIEBERT INC, 140 HUGUENOT STREET, 3RD FL, NEW ROCHELLE, NY 10801 USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB RNA interference (RNAi) is a powerful strategy to **inhibit** gene expression through specific mRNA degradation mediated by small interfering RNAs (siRNAs). In vivo, however, the application of siRNAs is severely limited by their instability and poor delivery into target cells and target tissues. Glioblastomas are the most frequent and malignant brain tumors with, so far, limited treatment options. To develop novel and more efficacious therapies, advanced targeting strategies against glioblastoma multiforme (GBM)-relevant target genes must be established in vivo. Here we use RNAi-based targeting of the secreted growth factor pleiotrophin (PTN), employing a polyethylenimine (PEI)/siRNA complex strategy. We show that the complexation of chemically unmodified siRNAs with PEI leads to the formation of complexes that condense and completely cover siRNAs as determined by atomic force microscopy (AFM). On the efficient cellular delivery of these PEI/siRNA complexes, the PTN downregulation in U87 glioblastoma cells in vitro results in decreased proliferation and soft agar colony formation. More importantly, in vivo treatment of nude mice through systemic application (subcutaneous or

intraperitoneal) of PEI-complexed PTN siRNAs leads to the delivery of intact siRNAs into subcutaneous tumor xenografts and a significant inhibition of tumor growth without a measurable induction of siRNA-mediated immunostimulation. Likewise, in a clinically more relevant orthotopic mouse glioblastoma model with U87 cells growing intracranially, the injection of PEI-complexed PTN siRNAs into the CNS exerts antitumoral effects. In conclusion, we present the PEI complexation of siRNAs as a universally applicable platform for RNAi in vitro and in vivo and establish, also in a complex and relevant orthotopic tumor model, the potential of PEI/siRNA-mediated PTN gene targeting as a novel therapeutic option in GBM.

L26 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN

2005:71066 Document No. 142:170050 DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors. Blenis, John; Murphy, Leon O. (President and Fellows of Harvard College, USA). PCT Int. Appl. WO 2005007090 A2 20050127, 104 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US21514 20040702. PRIORITY: US 2003-484761P 20030703.

AB Mitogen-activated protein (MAP) kinases (e.g., ERK1/2) phosphorylate a variety of target proteins including, for example, several immediate-early gene products (e.g., Fos, Myc, and Jun family proteins). Certain phosphorylation reactions require binding of the MAP kinase to the DEF domain of the target protein. Inhibitors that block this interaction may be useful therapeutics for human disease, including as antineoplastic agents. This invention provides several advantages over known therapies that directly target the MAP kinase signaling cascade. Typically, most compds. that **inhibit** the MAP kinase pathway are non-specific and **inhibit** more than one enzyme, and the targeted inhibited kinases are not available to perform normal physiol. functions necessary for cell survival, whereas therapeutic methods of the present invention **inhibit** the activation of particular target proteins and leave the MAP kinases enzymically active and available to phosphorylate other non-DEF domain-containing proteins. Thus, DEF domains are identified in a large number of proteins, and the principles of the invention are exemplified using the immediate-early gene, c-Fos. Screening assays useful for identifying compds. that **inhibit** the MAP kinase-DEF domain interaction are also disclosed.

L26 ANSWER 5 OF 8 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

2005:590535 The Genuine Article (R) Number: 932MN. Characterization of heparin affin regulatory peptide signaling in human endothelial cells. Polykratis A; Katsoris P; Courty J; Papadimitriou E (Reprint). Univ Patras, Dept Pharm, Mol Pharmacol Lab, Patras 26504, Greece (Reprint); Univ Patras, Dept Biol, Div Genet, Patras 26504, Greece; Univ Paris 12, CNRS, UMR 7149, Lab Rech Croissance Cellulaire, F-94010 Creteil, France. epapad@upatras.gr. JOURNAL OF BIOLOGICAL CHEMISTRY (10 JUN 2005) Vol. 280, No. 23, pp. 22454-22461. ISSN: 0021-9258. Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3996 USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Heparin affin regulatory peptide (HARP) is an 18-kDa secreted growth factor that has a high affinity for heparin and a potent role on tumor growth and **angiogenesis.** We have previously reported that HARP is mitogenic for different types of endothelial cells and also affects cell migration and differentiation (12). In this study we examined the signaling pathways involved in the migration and tube formation on

matrigel of human umbilical vein endothelial cells (HUVEC) induced by HARP. We report for the first time that receptor-type protein- tyrosine phosphatase β/ζ (RPTP β/ζ), which is a receptor for HARP in neuronal cell types, is also expressed in HUVEC. We also document that HARP signaling through RPTPβ/ζ leads to activation of Src kinase, focal adhesion kinase, phosphatidylinositol 3-kinase, and Erk1/2. Sodium orthovanadate, chondroitin sulfate-C, PP1, wortmannin, LY294002, and U0126 **inhibit** HARP-mediated signaling and HUVEC migration and tube formation. In addition, RPTPβ/ζ suppression using small interfering RNA technology interrupts intracellular signals and HUVEC migration and tube formation induced by HARP. These results establish the role of RPTPβ/ζ as a receptor of HARP in HUVEC and elucidate the HARP signaling pathway in endothelial cells.

L26 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN
2004:1019512 Document No. 141:423322 Neutralizing monoclonal antibody to pleiotrophin. Tso, J. Yun; Wellstein, Anton; Chao, Debra (USA). U.S. Pat. Appl. Publ. US 2004234519 A1 20041125, 38 pp. (English). CODEN: USXXCO. APPLICATION: US 2004-812366 20040326. PRIORITY: US 2003-458459P 20030326.

AB The authors disclose the preparation and characterization of antibodies that recognize pleiotrophin. The antibodies can **inhibit** cancer cell growth and **angiogenesis** in vitro or in vivo. The present invention provides for methods of inhibiting cancer cell growth or **angiogenesis** in a subject comprising administering to said subject an effective amount of the antibodies described herein.

L26 ANSWER 7 OF 8 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
2004:168354 Document No.: PREV200400162166. Pleiotrophin signal disruption of cell-cell adhesion, translocation of beta-catenin to the nucleus, and association of beta-catenin with different transcription activators in pleiotrophin-stimulated cells. Pinera, Pablo Perez [Reprint Author]; Deuel, Thomas F. [Reprint Author]; Vega-Alvarez, Jose A.. Molecular and Experimental Medicine, Scripps Research Institute, La Jolla, CA, USA. Blood, (November 16 2003) Vol. 102, No. 11, pp. 201b. print. Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology. CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB Pleiotrophin (PTN) is a 136 amino acid cytokine and the product of a proto-oncogene. It is expressed in a temporally restricted manner in different tissues including the vascular system during development but in adults it is expressed in only a few cell types. Pleiotrophin signals tumor **angiogenesis** and rapid tumor growth when it is introduced in different tumor cells and studied as tumor xenografts in vivo and Ptn gene expression is found in different human tumors, suggesting the potential of PTN to contribute to tumor promotion and as a mediator of an angiogenic switch. To seek a mechanism by which PTN signals tumor **angiogenesis** and tumor promotion, we previously identified an interaction of PTN with the Receptor Protein Tyrosine Phosphatase (RPTP) beta/zeta and demonstrated that PTN functions to **inhibit** its catalytic activity. We have also found that RPTP beta/zeta associates with **Anaplastic Lymphoma Kinase** (ALK) and beta-catenin, and furthermore that beta-catenin is a substrate for ALK, tyrosine phosphorylated beta-catenin is a substrate for RPTP beta/zeta, and in PTN-stimulated cells the steady-state levels of tyrosine phosphorylation of beta-catenin are rapidly and strikingly increased. We now demonstrate that PTN-stimulated cells disrupt the adherent cadherin-beta-catenin-alpha-catenin-actin cytoskeleton adhesion complex and lose cell-cell adhesion. We further demonstrate that PTN-stimulated cells import beta-catenin into the nucleus and that nuclear beta-catenin associates with different transcription activators than in nuclei of non-PTN-stimulated cells. We conclude that PTN signaling strikingly alters cell-cell adhesion and likely initiates different signaling pathways through the different interactions of beta-catenin with transcription activators in PTN-stimulated cells and suggest these

properties of PTN-stimulated cells may account for the more aggressive growth phenotype in tumor cells that acquire an activated Ptn gene during tumor progression.

L26 ANSWER 8 OF 8 MEDLINE on STN DUPLICATE 1
2002482179. PubMed ID: 12122009. Midkine binds to **anaplastic lymphoma kinase** (ALK) and acts as a growth factor for different cell types. Stoica Gerald E; Kuo Angera; Powers Ciaran; Bowden Emma T; Sale Elaine Buchert; Riegel Anna T; Wellstein Anton. (Lombardi Cancer Center, Georgetown University, Washington, D. C. 20007, USA.) The Journal of biological chemistry, (2002 Sep 27) Vol. 277, No. 39, pp. 35990-8. Electronic Publication: 2002-07-16. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.
AB Midkine (MK) is a developmentally regulated, secreted growth factor homologous to pleiotrophin (PTN). To investigate the potential role of MK in tumor growth, we expressed MK in human SW-13 cells and studied receptor binding, signal transduction, and activity of MK. The MK protein stimulates soft agar colony formation in vitro and tumor growth of SW-13 cells in athymic nude mice, as well as proliferation of human endothelial cells from brain microvasculature and umbilical vein (HUVEC) in the low ng/ml range. MK binds to **anaplastic lymphoma kinase** (ALK), the receptor for PTN, with an apparent K(d) of 170 pm in intact cells, and this receptor binding of MK is competed by PTN with an apparent K(d) of approximately 20 pm. Monoclonal antibodies raised against the extracellular ligand-binding domain of ALK **inhibit** ALK receptor binding of MK as well as MK-stimulated colony formation of SW-13 cells. Furthermore, MK stimulates ALK phosphorylation in WI-38 human fibroblasts and activates PI3-kinase and MAP kinase signal transduction in WI-38, HUVEC, neuroblastoma (SH SY-5Y) and glioblastoma (U87MG) cells that express the ALK protein. We conclude that MK can act as a growth, survival, and angiogenic factor during tumorigenesis and signals through the ALK receptor.

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L27 1262 (COURTY J?/AU OR BARRITAULT D?/AU OR PIERROT I?/AU OR DELBE J?/AU OR MILHIET P?/AU)

=> s l27 and HARP
L28 142 L27 AND HARP

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L29 33 L28 AND INHIBIT

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L30 24 L29 AND ANGIOGENESIS

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PROCESSING COMPLETED FOR L30
L31 8 DUP REMOVE L30 (16 DUPLICATES REMOVED)

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L31 ANSWER 1 OF 8 MEDLINE on STN DUPLICATE 1
2006658193. PubMed ID: 17091770. Effect of heparin affin regulatory peptide on the expression of vascular endothelial growth factor receptors in endothelial cells. Kokolakis G; Mikelis C; Papadimitriou E; **Courty J**; Karetsou E; Katsoris P. (Laboratory of Molecular Pharmacology, Department of Pharmacy, University of Patras, Greece.) In vivo (Athens, Greece), (2006 Sep-Oct) Vol. 20, No. 5, pp. 629-35. Journal code: 8806809. ISSN: 0258-851X. Pub. country: Greece. Language: English.
AB BACKGROUND: Heparin affin regulatory peptide (**HARP**) is an 18-kDa secreted protein that has been implicated in tumor growth and **angiogenesis**, although the mechanisms involved remain largely

unknown. In the present work, the effect of human recombinant **HARP** on the expression of the vascular endothelial growth factor (VEGF) receptors KDR, Flt-1 and neuropilin-1 was studied in cultured human umbilical vein endothelial cells (HUVEC). MATERIALS AND METHODS: The mRNA and protein levels of VEGF receptors were estimated by semi-quantitative RT-PCR and Western blot, respectively. Cell proliferation and migration were measured by MTT, direct counting of the cells and modified Boyden chamber assays. RESULTS: **HARP** decreased the expression of KDR but increased the expression of Flt-1 and neuropilin-1 at both the mRNA and protein level. The effect reached a maximum 4 h after the addition of **HARP** into the cell culture medium and was reversed at later time-points. When **HARP** was added to the culture medium 4 h before the addition of VEGF165, it inhibited VEGF165-induced proliferation and migration of HUVEC. CONCLUSION: These data suggest that **HARP** affects the expression of VEGF receptors and **inhibits** VEGF165-induced activation of HUVEC.

L31 ANSWER 2 OF 8 MEDLINE on STN DUPLICATE 2

2005290929. PubMed ID: 15797857. Characterization of heparin affin regulatory peptide signaling in human endothelial cells. Polykratis Apostolos; Katsoris Panagiotis; **Courty Jose**; Papadimitriou Evangelia. (Laboratory of Molecular Pharmacology, Department of Pharmacy, University of Patras, 26504 Patras, Greece.) The Journal of biological chemistry, (2005 Jun 10) Vol. 280, No. 23, pp. 22454-61. Electronic Publication: 2005-03-28. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Heparin affin regulatory peptide (**HARP**) is an 18-kDa secreted growth factor that has a high affinity for heparin and a potent role on tumor growth and **angiogenesis.** We have previously reported that **HARP** is mitogenic for different types of endothelial cells and also affects cell migration and differentiation (12). In this study we examined the signaling pathways involved in the migration and tube formation on matrigel of human umbilical vein endothelial cells (HUVEC) induced by **HARP.** We report for the first time that receptor-type protein-tyrosine phosphatase beta/zeta (RPTPbeta/zeta), which is a receptor for **HARP** in neuronal cell types, is also expressed in HUVEC. We also document that **HARP** signaling through RPTPbeta/zeta leads to activation of Src kinase, focal adhesion kinase, phosphatidylinositol 3-kinase, and Erk1/2. Sodium orthovanadate, chondroitin sulfate-C, PP1, wortmannin, LY294002, and U0126 **inhibit HARP**-mediated signaling and HUVEC migration and tube formation. In addition, RPTPbeta/zeta suppression using small interfering RNA technology interrupts intracellular signals and HUVEC migration and tube formation induced by **HARP.** These results establish the role of RPTPbeta/zeta as a receptor of **HARP** in HUVEC and elucidate the **HARP** signaling pathway in endothelial cells.

L31 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN

2004:370799 Document No. 140:386013 **Angiogenesis**-inhibiting **HARP** factor peptide fragments. **Courty, Jose**; **Barritault, Denis**; Bernard Pierrot, Isabelle Christine; **Delbe, Jean Camille Georges**; **Milhiet, Pierre Emmanuel** (Centre National de la Recherche Scientifique CNRS, Fr.). Fr. Demande FR 2846659 A1 20040507, 36 pp. (French). CODEN: FRXXBL. APPLICATION: FR 2002-13621 20021030.

AB The invention relates to peptide fragments 13-39 and 65-97 of the factor **HARP**, which **inhibit angiogenesis.** In an advantageous way, these peptides can be peptide 111-136 of **HARP.** The invention also relates to pharmaceutical compns. including these peptides or of the nucleic acids coding for these peptides, and their uses for the treatment of pathologies associated with **angiogenesis**, in particular proliferative disorders like cancer.

L31 ANSWER 4 OF 8 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights

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2004256915 EMBASE Identification of heparin affin regulatory peptide domains with potential role on **angiogenesis.** Polykratis A.; **Delbe J.**; **Courty J.**; Papadimitriou E.; Katsoris P.. E. Papadimitriou, Laboratory of Molecular Pharmacology, Department of Pharmacy, University of Patras, Patras, GR 26504, Greece. epapad@upatras.gr. International Journal of Biochemistry and Cell Biology Vol. 36, No. 10, pp. 1964-1976 Oct 2004.
Refs: 38.
ISSN: 1357-2725. CODEN: IJBBFU
S 1357-2725(04)00083-4. Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 20040709. Last Updated on STN: 20040709

AB Heparin affin regulatory peptide (**HARP**) is a growth factor displaying high affinity for heparin. It is present in the extracellular matrix of many tissues, interacting with heparan sulfate and dermatan/chondroitin sulfate glycosaminoglycans. We have previously shown that **HARP** is implicated in the control of **angiogenesis** and its effects are mimicked, at least in part, by synthetic peptides that correspond to its N and C termini. In the present work, we show that **HARP** is cleaved by plasmin, leading to the production of five peptides that correspond to distinct domains of the molecule. Heparin, heparan sulfate and dermatan sulfate, at various **HARP** to glycosaminoglycan ratios, partially protect **HARP** from plasmin degradation. The molecules with higher affinity to **HARP** are the more protective, heparin being the most efficient. The peptides that are produced from cleavage of **HARP** by plasmin, affect in vivo and in vitro **angiogenesis** and modulate the angiogenic activity of vascular endothelial growth factor on human umbilical vein endothelial cells. Similar results were obtained in vitro with recombinant **HARP** peptides, identical to the peptides generated after treatment of **HARP** with plasmin. These results suggest that different regions of **HARP** may induce or **inhibit** **angiogenesis.** .COPYRGT. 2004 Elsevier Ltd. All rights reserved.

L31 ANSWER 5 OF 8 MEDLINE on STN DUPLICATE 3

2004302962. PubMed ID: 15203110. Identification of heparin affin regulatory peptide domains with potential role on **angiogenesis.** Polykratis Apostolos; **Delbe Jean**; **Courty Jose**; Papadimitriou Evangelia; Katsoris Panagiotis. (Laboratory of Molecular Pharmacology, Department of Pharmacy, University of Patras, Patras, GR 26504, Greece.) The international journal of biochemistry & cell biology, (2004 Oct) Vol. 36, No. 10, pp. 1954-66. Journal code: 9508482. ISSN: 1357-2725. Pub. country: England: United Kingdom. Language: English.

AB Heparin affin regulatory peptide (**HARP**) is a growth factor displaying high affinity for heparin. It is present in the extracellular matrix of many tissues, interacting with heparan sulfate and dermatan/chondroitin sulfate glycosaminoglycans. We have previously shown that **HARP** is implicated in the control of **angiogenesis** and its effects are mimicked, at least in part, by synthetic peptides that correspond to its N and C termini. In the present work, we show that **HARP** is cleaved by plasmin, leading to the production of five peptides that correspond to distinct domains of the molecule. Heparin, heparan sulfate and dermatan sulfate, at various **HARP** to glycosaminoglycan ratios, partially protect **HARP** from plasmin degradation. The molecules with higher affinity to **HARP** are the more protective, heparin being the most efficient. The peptides that are produced from cleavage of **HARP** by plasmin, affect in vivo and in vitro **angiogenesis** and modulate the angiogenic activity of vascular endothelial growth factor on human umbilical vein endothelial cells. Similar results were obtained in vitro with recombinant **HARP** peptides, identical to the peptides generated after treatment of **HARP** with plasmin. These results suggest that different regions of **HARP** may induce or **inhibit** **angiogenesis.**

L31 ANSWER 6 OF 8 MEDLINE on STN DUPLICATE 4
2004111756. PubMed ID: 15001987. Heparin affin regulatory peptide binds to vascular endothelial growth factor (VEGF) and **inhibits** VEGF-induced **angiogenesis.** Heroult Melanie; Bernard-Pierrot Isabelle; **Delbe Jean**; Hamma-Kourbali Yamina; Katsoris Panagiotis; **Barritault Denis**; Papadimitriou Evangelia; Plouet Jean; **Courty Jose.** (Laboratoire de Recherche sur la Croissance Cellulaire, la Reparation et la Regeneration Tissulaires (CRRET), FRE CNRS 2412, Universite Paris XII-Val de Marne, Avenue du General de Gaulle, 94010 Creteil, France.) Oncogene, (2004 Mar 4) Vol. 23, No. 9, pp. 1745-53. Journal code: 8711562. ISSN: 0950-9232. Pub. country: England: United Kingdom. Language: English.

AB Heparin affin regulatory peptide (**HARP**) is an heparin-binding molecule involved in the regulation of cell proliferation and differentiation. Here, we report that **HARP** inhibited the biological activity induced by the 165-amino-acid form of vascular endothelial growth factor (VEGF165) on human umbilical vein endothelial cells. Endothelial-cell proliferation induced by VEGF165 showed about 50% inhibition in the presence of **HARP** in a concentration of 3 nM. In similar range of concentrations, **HARP** blocked tube formation induced by VEGF165 in three-dimensional **angiogenesis** assay. In vivo studies showed that **HARP** inhibited the VEGF165-induced Matrigel trade mark infiltration of endothelial cells. We then investigated the mechanisms of this inhibition and shown that **HARP** inhibited the binding of 125I-VEGF165 to the VEGF receptors of endothelial cells. Additional studies using VEGF soluble receptors indicated that binding of 125I-VEGF165 to kinase insert domain-containing receptor and neuropilin receptor was inhibited by **HARP**, but conversely the binding of 125I-VEGF165 to fms-like tyrosine kinase I receptor was unaffected. A competitive affinity-binding assay demonstrated that **HARP** interacted directly with VEGF165 with a dissociation coefficient of 1.38 nM. Binding assay using deletion mutants of **HARP** revealed that the thrombospondin type-1 repeats domains were involved in this interaction. These data demonstrate for the first time that the angiogenic factor **HARP** can also negatively regulates the angiogenic activity of VEGF165.

L31 ANSWER 7 OF 8 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN DUPLICATE 5
2004113415 EMBASE A Synthetic Peptide that Corresponds to the C-terminal Region of **HARP Inhibits Angiogenesis** in vivo and in vitro. Mikelis K.; Polykratis A.; Zompra A.; Cordopatis P.; Katsoris P.; **Courty J.**; Papadimitriou E.. K. Mikelis, Lab. of Molecular Pharmacology, Dept. of Pharmacy, University of Patras, Patra, GR 26504, Greece. Review of Clinical Pharmacology and Pharmacokinetics, International Edition Vol. 18, No. 1, pp. 144-145 2004.
Refs: 9.
ISSN: 1011-6583. CODEN: EKIEE2
Pub. Country: Greece. Language: English. Summary Language: English.
Entered STN: 20040412. Last Updated on STN: 20040412

AB Heparin Affin Regulatory Peptide (**HARP**), also known as pleiotrophin or heparin-binding growth-associated molecule, is an 18 kDa growth factor that has a high affinity for heparin. In the present work, we studied the effects of a synthetic peptide that corresponds to the last 25 amino-acids of the C-terminal region. In the in vivo chicken embryo chorioallantoic membrane model of **angiogenesis**, the peptide decreased the number of blood vessels in a dose-dependent manner. It also decreased the migration of human umbilical vein endothelial cells (HUVEC) in vitro, while it had no effect on HUVEC proliferation. Finally, the peptide also decreased the ability of HUVEC to form capillary-like networks when cultured on matrigel.

L31 ANSWER 8 OF 8 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
1995:353827 Document No.: PREV199598368127. Effect of Heparin on Bovine

Epithelial Lens Cell Proliferation Induced by Heparin Affin Regulatory Peptide. **Delbe, J.**; Vacherot, F.; Laaroubi, K.; **Barritault, D.** [Reprint author]; **Courty, J.**. Lab. CRRET, Univ. Paris Val-de Marne, Ave. General Gaulle, 94010 Creteil Cedex, France. Journal of Cellular Physiology, (1995) Vol. 164, No. 1, pp. 47-54. CODEN: JCLLAX. ISSN: 0021-9541. Language: English.

AB **HARP** (heparin affin regulatory peptide) is an 18 kDa heparin binding protein, also known as HB-GAM or pleiotrophin (PTN) which has been primarily isolated from brain and uterus, and displays neurite outgrowth, angiogenic and mitogenic activities. Previously, we have expressed the human cDNA encoding human **HARP** in NIH 3T3 cells. Purified recombinant **HARP** displayed mitogenic activity for endothelial cells. Its NH2-terminal sequence indicates that the **HARP** molecule possesses a three amino acid extension from the signal peptide more than the NH2-terminal described. For HB-GAM or PTN, these three amino acids may be essential for the stability and the mitogenic activity of this growth factor. In an attempt to further study the mode of action of this growth factor, we have investigated the mitogenic effect of **HARP** on various cell types. In contrast to FGF-2, **HARP** failed to induce stimulation of DNA synthesis on a CCL39 cell line. However, we found that in quiescent bovine epithelial lens (BEL) cells, the stimulation of DNA synthesis induced by **HARP** is dose-dependent (EC-50: 2.5 ng/ml) and maximal stimulation is as potent as that induced by FGF-2 (EC-50: 25 pg/ml). Interestingly, when BEL cells were allowed to quiesce in the presence of serum, the stimulation induced by **HARP** is considerably less potent. In this highly responsive cell system, heparin could potentiate the mitogenic activity of **HARP** at very low doses (0.1-1 mu-g/ml) and **inhibit** this activity at concentrations of 10 mu-g/ml. In contrast to its protective effect on FGF-1 and -2, heparin was unable to preserve **HARP** from tryptic and chymotryptic degradations.

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